REMARKS

Claims 1, 13, 14, 19, 24, 25, 26, and 27 have been amended for greater clarity and to define the invention more particularly. Support for the claim amendments can be found throughout the specification (see, e.g., page 16, lines 11-16) and original claims. No new matter has been introduced.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Applicants note that the Examiner has withdrawn the rejections under 35 U.S.C. § 101, § 112, 1st paragraph, and § 112, 2nd paragraph, in view of Applicants' Response and Amendment filed on July 20, 2005.

Objection to Claims

The Examiner objects to withdrawn claim 14 for lacking a terminal period. Applicants have amended claim 14 to obviate the objection.

Objection to the Specification

The Office Action asserts that SEQ ID Nos. are missing for the sequences in the figures. In response, Applicants have amended the specification by identifying each of the sequences in Figures 2-6 with a SEQ ID NO, thereby obviating this objection.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 19 and 24-27 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner states that this is a new matter rejection.

First, the Office Action asserts that the limitation "at least 65% identical" in claim 19 is not supported by the application (see Office Action, page 3, lines 3-4). Applicants respectfully disagree.

Applicants already pointed out in the Response filed on July 2, 2003 that the above limitation is fully supported by the original specification. For example, seven isolated miniature protein sequences shown in Figure 4 fall in the scope of claim 19. Applicants also provided a sequence alignment of the seven peptide sequences (see **Exhibit 5** in the Response filed on July 2, 2003). The sequence listing indicates that SEQ ID NO: 23 (the partial sequence of clone 4100) shares at least 68.8% sequence identity with the other six peptide sequences in Figure 4.

Nevertheless, without acquiescing to the Examiner's assertion, Applicants have amended claim 19 to recite "at least 90% identical." Support for claim 19 can be found throughout the specification (see, e.g., page 16, lines 11-16). Applicants submit that the claim amendments are made solely to focus on aspects of greatest current commercial interest. Applicants reserve the right to pursue the claims of similar or differing scope in the future.

Second, the Office Action rejects claims 24-27 because "the resulting modified protein may have this property [binds to the Bcl-X_L or Bcl2 protein], the unsubstituted protein does not" (see Office Action, page 3, lines 5-10). Solely for greater clarity, Applicants have amended claims 24-27 to recite the "modified" avian pancreatic polypeptide.

Third, the Office Action rejects claim 24-27 because "the specification discloses only the scaffold aPP of SEQ ID NO: 6 with SEQ ID NOs: 23-29 grafted on it, [but] does not disclose any other avian pancreatic polypeptides comprising these sequences or modified to produce these peptide" (see Office Action, page 3, lines 12-13). Applicants respectfully disagree.

Applicants submit that the specification makes it clear that the term "avian pancreatic polypeptide" (aPP) refers to only one particular scaffold protein having SEQ ID NO: 6. For example, the specification teaches that "[e]xamples of these miniproteins include . . . the thirty-six amino acid protein, avian pancreatic peptide (Zondlo & Schepartz, (1999) Am. Chem. Soc. 121, 6938-6939). Avian pancreatic polypeptide (aPP) is a polypeptide in which residues fourteen through thirty-two form an alpha helix stabilized by hydrophobic contacts with an N-terminal type II polyproline (PPII) helix formed by residues one through eight. Because of its small size and stability, aPP is an excellent scaffold for protein grafting of alpha helical recognition epitopes (Zondlo & Schepartz, (1999) J. Am. Chem. Soc. 121, 6938-6939)" (page 3,

lines 4-12). Based on the teachings of the specification and the general knowledge in the art, one of skill in the art would readily understand that the term "avian pancreatic polypeptide" means the unique aPP protein; there are no other avian pancreatic polypeptides as asserted by the Examiner.

In light of the detailed description provided in the specification, one of skill in the art would readily appreciate that Applicants were in possession of the claimed invention at the time this application was filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections for lack of written description.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-5, 12-14, 19, and 23-27 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants respectfully disagree.

Specifically, although the Office Action acknowledges that the specification is enabling for SEQ ID NOS: 23-29, the Office Action asserts that the specification does not reasonably provide enablement for avian pancreatic polypeptides with the stated substitutions and properties. In particular, the Office Action asserts that "peptides of SEQ ID NOS: 27, 28, and 29 do not bind Bcl. As such, claim 26 and 27 embrace clearly inoperative embodiments." Finally, the Office Action asserts that the specification does not identify any other avian pancreatic polypeptides that could be modified. See Office Action, page 3, lines 15-21; page 4, lines 1-16.

As an initial matter, Applicants respectfully submit that the Examiner has incorrectly characterized the claimed invention. Peptides of SEQ ID NOS: 27, 28, and 29 were identified from phage display screenings based on their ability to bind to a Bcl2 protein. For example, the specification teaches that "[t]he phage library BAKLIB was subjected to five rounds of panning against immobilized GST-Bcl-2. The percent retention of the phage library increased 225-fold over the course of the selection from 0.01% in the first round to 2.25% in the fifth round" (see, e.g., page 38, lines 25-32). Although the specification does not provide dissociation constants (Kd) for these three peptides, these peptides **do** bind to Bcl2, contrary to the Examiner's assertion.

In addition, Applicants have argued above that the specification makes it clear that the term "avian pancreatic polypeptide" (aPP) refers to only one particular scaffold protein having SEQ ID NO: 6, and one of skill in the art would readily know that the term "avian pancreatic polypeptide" does not include any other avian pancreatic polypeptides. Thus, the claims do provide a base structure (i.e., the aPP) to modify, contrary to the Examiner's assertion.

Further, Applicants point out that "[c]ompliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic.'" Further, "[t]he specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount experimentation. *In re Borkowski*, 442, F.2d 904, 908, 164 USPQ 642,645 (CCPA 1970)." See MPEP 2164.02.

Independent claims 1 and 19 as amended relate to modified aPP polypeptides which are structurally and functionally defined. The claims specify that these modified aPP polypeptides derive from the aPP scaffold protein and bind to a Bcl-2 protein. Specifically, the specification teaches how to modify the aPP in order to arrive at the claimed invention. For example, claim 1 specifies that an avian pancreatic polypeptide is modified by substitution of at least one amino acid residue, said at least one residue being exposed on the alpha helix domain of the polypeptide when the polypeptide is in a tertiary form, wherein said at least one substituted residue is selected from a site on a known protein through which interaction with a Bcl2 protein occurs.

In particular, the specification provides working examples to show functional selection of protein-binding miniature proteins from an aPPBAK library by phage display screenings (see, e.g., Examples 12-16 on pages 37-42). The specification teaches that the aPPBAK library was made by mutagenesis within the aPP scaffold protein using the NNS codon scheme and provides the degenerate sequence of the library (see SEQ ID NO: 16). The phagemid clones were identified from the aPPBAK library by their ability to bind to a Bcl-2 protein. Although Figure 4 only shows 7 sequences (SEQ ID NOS: 23-29) which were sequenced and analyzed, a larger number of clones were actually identified from the library with the same properties. For example, the specification describes that "[a]fter five rounds **sixteen** phagemid library clones were sequenced. The selected sequences (Fig. 4) show a high degree of convergence. Seven

distinct sequences were isolated with four sequences represented multiple times." Based on the detailed teachings of the specification and the knowledge in the art, a skilled artisan would readily identify further modified aPP polypeptides with the properties as claimed.

In view of the above, Applicants submit that the specification provides enablement for the pending claims as amended, and undue experimentation would not be required. Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections for lack of enablement.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 13 and 23 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

First, the Office Action asserts that the recitation in claim 13 "wherein the interaction between the known protein and the Bcl2 protein is inhibited" is confusing. Solely to expedite prosecution, Applicants have amended claim 13 to clarify that "wherein the interaction between the known protein and the Bcl2 protein is inhibited by the modified avian pancreatic polypeptide," thereby rendering the rejection moot.

Second, the Office Action asserts that claim 23 is confusing in its dependency on claim 12 because the "known protein" in claim 12 is identified as Bcl-2, while claim 23 recites Bak. Applicants respectfully disagree.

Applicants already pointed out in the previous response that the term "a Bcl2 protein" in claims 1 and 12 is readily understood in the art to refer to any member of the Bcl2 family, which includes Bcl2 protein and other Bcl2 family members such as Bcl-X_L, Bid, Bax, Bad, and Bak. For example, the specification teaches that the claimed aPP miniature protein binds to both Bcl2 and Bcl-X_L (e.g., page 14, lines 21-32; page 41, lines 1-14). In addition, the Bcl2 family was well known at the time the application was filed (see, e.g., page 39, lines 13-15). Further, it was

known in the art that the Bcl2 family members bind to each other (homodimerize or heterodimerize).

Accordingly, claim 23 correctly depends from claim 12 since Bak in claim 23 is a member of the Bcl2 family. Indeed, the specification teaches selection of residues from Bak as a known protein for substitution of residues on aPP. Applicants previously presented in the Declaration additional data to show that another Bcl2 family member, Bad (like Bak, a known Bcl2-binding protein), can be effectively used for making Bcl2-binding miniature proteins as claimed by the present invention.

In view of the above, Applicants submit that all pending claims are clear and definite. Reconsideration and withdrawal of rejections under 35 U.S.C. § 112, second paragraph, are respectfully requested.

Claim Rejections under 35 U.S.C. § 102

Claim 1-5, 12-13, and 23-25 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Chittenden et al. (U.S. Patent No. 5,656,725). Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that "[t]he claims recite no specific base structure or sequence that is modified nor a particular structure or sequence that results. No particular avian pancreatic polypeptide is recited as the base structure to be modified and no particular SEQ ID NO. is recited identifying the resulting product" (see Office Action, page 5, lines 16-19).

Applicants respectfully disagree with the Examiner's claim construction of the term "avian pancreatic polypeptide." Applicants have argued above that the specification makes it clear that the term "avian pancreatic polypeptide" (aPP) refers to only one particular scaffold protein having SEQ ID NO: 6, and the term "avian pancreatic polypeptide" does not include any other avian pancreatic polypeptides because there are no such polypeptides specified. In view of the teachings of the specification, one of ordinary skill in the art would not construe the claims as

the Examiner suggests, but rather, the skilled artisan would know the metes and bounds of the term "avian pancreatic polypeptide."

Further, Applicants wish to draw the Examiner's attention to a recent Federal Circuit decision *Phillips v. AWH Corp.*, 2005 WL 1620331 (Fed. Cir. July 12, 2005). In this opinion, the *en banc* majority holds that when construing patent claims, a court should **consult the specification** and prosecution history to determine if the patentee intended to use particular terms in ways other than their ordinary meaning. Thus, Applicants respectfully submit that the Examiner's claim construction is not consistent with the teachings of the specification.

Chittenden et al. merely teach a fragment (SEQ ID NO: 10) of the Bak protein that binds to Bcl-X_L. Although Chittenden's SEQ ID NO: 10 arguably matches 9 of 15 amino acids of instant SEQ ID NO: 23, Chittenden et al. do not teach any sequence that derives from the base structure of avian pancreatic polypeptide (aPP, SEQ ID NO: 6). In contrast, the present invention is drawn to modified **avian pancreatic polypeptides** by substitution of at least one amino acid residue.

In order for a prior art reference to be a proper reference under 35 U.S.C. § 102, the prior art reference must teach each and every element of the present invention. Independent claims 1 and 19 are not anticipated by Chittenden et al. because Chittenden et al. fail to teach all the limitations of the instant claims. For the same reasons, all claims depending from claims 1 or 19 are not anticipated by Chittenden et al. Therefore, reconsideration and withdrawal of rejections under 35 U.S.C. § 102 are respectfully requested.

Claim Rejections under 35 USC § 103(a)

Claims 1-5, 12-13, and 23-25 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Zondlo et al. (J. Am. Chem. Soc. 121:6938-939) in view of Sattler et al. (Science, 275:983-986, 1997). Applicants respectfully traverse this rejection.

Pursuant to MPEP 2143 and in view of *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), "[t]o establish a *prima facie* case of obviousness, three basic criteria must be

met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

Independent claim 1 is directed to an avian pancreatic polypeptide modified by substitution of at least one amino acid residue, said at least one residue being exposed on the alpha helix domain of the polypeptide when the polypeptide is in a tertiary form, wherein said at least one substituted residue is selected from a site on a known protein through which interaction with a Bcl2 protein occurs, wherein said modified avian pancreatic polypeptide binds to the Bcl2 protein.

In contrast, Zondlo et al. teach use of avian pancreatic polypeptide (aPP) as a scaffold to design miniature proteins that bind to certain **DNA** targets with high specificity. Indeed, Zondlo et al. worked entirely with **DNA-binding** miniature proteins (see, e.g., Figures 1-3). However, Zondlo et al. do not teach or suggest miniature proteins that bind to a Bcl2 protein or any other protein target with high specificity. In particular, Zondlo et al. do not teach or suggest modifying aPP by substitution of at least one residue selected from a site on a known protein through which interaction with a Bcl2 protein occurs.

Sattler et al. describe that a region (amino acids 72-87) of the Bak protein interacts with Bcl-X_L. Sattler et al. are completely silent on designing miniature proteins through modifying aPP by substitution. Further, Sattler et al. simply do not teach or suggest selection of residues from the Bak protein for protein grafting purposes. Thus, Sattler et al. fail to bridge the gap between Zondlo et al. and the present invention.

Accordingly, Applicants submit that neither Zondlo et al. nor Sattler et al. teach or suggest all the claim limitations. Even if combined, these cited references do not teach all the elements of the invention of independent claim 1.

In addition, Applicants respectfully submit that the cited references, taken singly or in combination, do not provide an incentive or motivation to make the combination. The Examiner seems to argue that Zondlo et al. provide motivation by stating that "[t]his strategy may represent a general approach to the design of small, folded proteins that recognize nucleic acid and **protein** targets with high affinity and specificity" (Zondlo et al., page 6938, the last sentence of the first paragraph, emphasis added). Applicants respectfully disagree for the following reasons.

Applicants stress that Zondlo et al. worked entirely with **DNA-binding** miniature proteins with high specificity, rather than protein-binding miniature proteins with high specificity. Although Zondlo et al. mention "protein targets" generally in only one sentence of the whole article, Zondlo et al. do not teach or suggest any specific protein target. Assuming *arguendo*, a skilled artisan were to design miniature proteins that recognize protein targets based on Zondlo's disclosure, there is absolutely no suggestion or motivation in the cited art to target a Bcl2 protein as recited in the instantly claimed invention. Reliance on the specification as filed for providing motivation to combine the two references is impermissible. M.P.E.P. § 706.02 (j) recites that "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not be based on applicant's disclosure. *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." Applicants submit that the Examiner has used improper hindsight to combine the references in this case.

Further, Applicants respectfully submit that the cited references, taken singly or in combination, do not provide any reasonable expectation of success in making Bcl2-binding miniature proteins with high specificity as claimed in the present invention. It was well known in the art that proteins and nucleic acids have different structural and functional properties. As a matter of fact, at the time this application was filed, the design of molecules that bind **protein** surfaces with high affinity and high specificity was, if not impossible, a major challenge for chemical biologists (see the first sentence of Chin et al., 2001, Angew. Chem. Int. Ed. 40(20): 3806-3809, enclosed herewith as **Exhibit A**; and references cited therein). Although Zondlo et al. generally mention protein targets, Zondlo et al. do not teach any specific protein target or provide any guidance on selection of residues for protein grafting. It is Applicants' position that

Zondlo et al. at best suggest that it may be "obvious to try" to design protein-binding miniature proteins with high specificity, but it does not imply that there was a reasonable expectation of success. Here, a reasonable expectation of success is being confused with a "hope of success."

In view of the above, none of the three requirements for establishing a *prima facie* case of obviousness has been satisfied. Accordingly, Applicants respectfully request reconsideration and withdrawal of all claim rejections under 35 U.S.C. 103(a).

CONCLUSION

In view of the foregoing amendments and remarks, the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7546. A two-month petition for extension of time and payment of the appropriate fee are being filed concurrently herewith. Applicants request that any further fees or any credits be applied to **Deposit Account No. 18-1945, under Order No. YU-P01-021.**

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Respectfully submitted,

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